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CASE REPORT

Expansion of range of joint motion following treatment of systemic sclerosis with tocilizumab

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Abstract Systemic sclerosis (SSc) presents stiffness of extremities due to sclerosis of the tissue especially at fingers, hands, and forearms. Here we report the case of a patient with diffuse cutaneous SSc who was administered anti-interleukin-6 receptor antibody tocilizumab (TCZ). Skin condition of SSc is evaluated by pinching the skin according to the Rodnan skin score, but sometimes tissue atrophy results in overestimation of the condition. To understand how the extremities softened after initiation of TCZ, we observed mobility of extremities. Range of motion (ROM) of joints was measured every four months after initiation of TCZ. The patient presented not only reduction of Rodnan score but also amelioration of mobility of extremities. The Rodnan skin score reduced from 35 to 7 within sixteen months, and ROM of most joints except ankle was expanded.

Keywords Systemic sclerosis · Tocilizumab · Range of joint motion

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Introduction

Systemic sclerosis (SSc) is a connective tissue disease that develops sclerotic changes in the skin and visceral organs. Patients present with stiffness of the limbs because of sclerosis in the skin and periarticular connective tissues. We present the case of a patient with SSc who showed improvement of joint motion after treatment with the anti-interleukin-6 (IL-6) receptor antibody tocilizumab (TCZ).

Although the etiology of SSc remains unclear, many factors have been proposed. IL-6 is a pleiotropic factor that plays a major role in inflammation; furthermore, it is a candidate factor that can reproduce the pathological conditions of SSc. Reportedly, culture supernatants of skin tissue or peripheral blood mononuclear cells from patients with SSc contain higher concentrations of IL-6 than those from normal controls [1, 2]. Elevation of serum IL-6 levels has also been reported, and these levels are reported to depend on skin score [3–5]. In addition, an anti-IL-6 antibody has been reported to suppress procollagen production by fibroblasts isolated from patients with SSc [6]. Given these facts, it is suggested that anti-IL-6 therapy may ameliorate the clinical symptoms of SSc. We have previously reported conventional therapy-resistant SSc cases that responded well to TCZ [7]. In our former study, two patients who were administered TCZ for six months showed a decrease in their modified Rodnan total skin (mRTS) scores, suggesting that their skin sclerosis could have been ameliorated by TCZ administration. However, the skin score in patients with SSc sometimes decreases spontaneously as a result of tissue atrophy. Therefore, it is necessary to examine not only the skin score but also the function of the extremities. In this case, we evaluated the range of motion (ROM) of joints before and after TCZ administration to investigate the effects of TCZ on mobility of extremities in a patient with SSc.

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Case report

A 59-year-old woman noticed Raynaud's phenomenon and swellings in her fingers in 2004. This skin sclerosis developed from her fingers and expanded to her face and feet. She became aware of dyspnea on exertion, dysphagia, and stiffness of the hands, wrists, elbows, and shoulders. Although both anti-Scl-70 and anti-centromere antibodies were negative, she was diagnosed with SSc because skin biopsy revealed thick and tight collagen fiber bundles in the dermis. Antinuclear antibody was positive at a titer of 1:1280 with a speckled pattern. Closer examination revealed that anti-RNA polymerase III antibody was positive. Treatment was initiated with prednisolone at 10 mg/day, and cyclosporine was then added to this regimen, which was otherwise ineffective. In 2005, the patient developed subacute renal failure and hypertension; therefore, dialysis therapy was indicated. After temocapril at dosage of 4 mg/day and telmisartan at dosage of 80 mg/day were administered, her condition stabilized and hemodialysis was terminated. In 2007, the patient exhibited recurrent dyspnea on exertion and inadequate oral intake as a result of recurrent ileus with pneumatosis cystoides intestinalis. For a while, home parenteral nutrition was used; however, prolonged administration of antibiotics proved effective only to a limited extent. Though endoscopic examination showed normal esophageal mucosa, measurement of esophageal pressure indicated absence of peristaltic waves during swallowing. Chest computed tomography (CT) images detected no significant interstitial modification, however echocardiogram revealed pericardial effusion and elevated peak pressure gradient of tricuspid regurgitation (28 mmHg). Since right heart catheterization showed elevation of mean pulmonary artery pressure (25 mmHg), treatment with 125 mg/day bosentan was initiated. Her visceral organs became involved as described; furthermore, the skin sclerosis spread to her trunk. Her mRTS score was 35 in 2008. The patient had to use a wheelchair to move about, and she was unable to propel it by herself. Because her activities of daily living (ADL) were severely compromised because of skin sclerosis, we applied for a TCZ project which was supported by the National Institute of Biomedical Innovation (Ibaraki City, Osaka, Japan). After receiving informed consent by the patient and approval by the Ethics Committee of Osaka University Hospital, we initiated TCZ treatment. Laboratory data at TCZ initiation are presented in Table 1. The administration dosage and schedule of TCZ was 8 mg/kg every four weeks, which corresponds to the regimen used for rheumatoid arthritis. The following medications were administered concurrently: methylprednisolone (8 mg/day), telmisartan (40 mg/day), furosemide (80 mg/day), beraprost (120 μg/day), omeprazole (20 mg/day), cefdinir (300 mg/day), and bosentan (125 mg/day). ROM of the metacarpophalangeal joints of the hands as well as that of the wrist, elbow, shoulder, knee, and ankle joints was measured every 4 months using a goniometer.

ROM of the knee, wrist, and shoulder joints after TCZ initiation are shown in Fig. 1. ROM values, except for those in ankles, improved during the observation period. Skin sclerosis also improved over the course of treatment, and the patient's mRTS score decreased from 35 to 7. She could walk independently once again. In patients with SSc, problems concerning joint motion may result from sclerotic changes in the skin and subcutaneous tissue. In this case, the patient's knee, wrist, and shoulder joints, which were drastically affected, showed tendencies toward an inverse

Table 1 Laboratory data before TCZ therapy initiation

Blood cell count			Urine test			Biochemical data		
White blood cells	(3300–9400)	5660/μL	pH	(5.0–8.0)	5.0	Creatinine	(0.5–0.9)	2.09 mg/dL
Red blood cells	(390–510 × 10^4)	383 × 10^4/μL	Urine gravity	(1.005–1.030)	1.008	Aspartate aminotransferase	(<40)	19 IU/L
Hemoglobin	(12.0–15.0)	9.9 g/dL	Protein	(−)	−	Alanine aminotransferase	(<40)	11 IU/L
Hematocrit	(35.0–45.0)	30.6 %	Sugar	(−)	−	Gamma glutamyl transpeptidase	(8–51)	12 IU/L
Mean corpuscular volume	(84.0–98.0)	79.8 fL	Urobilinogen	(+/−)	+/−	Lactate dehydrogenase	(103–229)	241 IU/L
Mean corpuscular hemoglobin	(28.0–33.0)	25.8 pg	Bilirubin	(−)	−	Amylase	(44–153)	212 IU/L
Mean corpuscular hemoglobin concentration	(31.0–35.0)	32.3 %	Ketone	(−)	−	Creatinine kinase	(54–286)	11 IU/L
			Occult blood	(−)	−	Cholesterol	(150–220)	177 mg/dL
Platelet	(130–320 × 10^3)	187 × 10^3/μL				Albumin	(3.6–4.7)	3.5 g/dL
						C-reactive protein	(0.0–0.2)	0.13 mg/dL

Values in parentheses indicate normal limits at our hospital

relationship with the skin scores of the areas adjacent to the joints (Fig. 2a–c). In contrast, although the skin scores of the lower legs and dorsum of the feet improved, ROM of the ankle joint remained unchanged (Fig. 2d).

Discussion

This case report describes a patient with SSc who showed impaired mobility in addition to severe skin sclerosis. TCZ administration proved beneficial for the skin sclerosis, as described previously [7]. However, patients with SSc sometimes show improvements in their poor skin scores because of skin atrophy, considering that the Rodnan skin score is obtained by pinching the skin. In our patient, however, we observed an improvement in mobility of the limbs as well as the skin score. The patient regained the ability to walk independently, proving that the improved skin score not only represented the ease of pinching the skin but also functional improvement.

Several factors may contribute to the improvement in ROM during TCZ treatment in the present case. First, TCZ might act on arthritis. TCZ is a recognized medication for arthritis; therefore, it may improve joint movement through amelioration of joint inflammation. The patient, however, showed neither swelling nor tenderness of the joints before and during TCZ treatment. In addition, her C-reactive protein level was normal. Therefore, the observed improvement in ROM was probably not because of arthritis remission. Second, the ROM improvements might be the natural course of the disease or might indicate atrophic change. Four years passed between the onset of disease and initiation of TCZ treatment, and disability of limbs was worsening during this period. The fact that ROM improvement in the knee and shoulder joints was detected within the first 4 months of TCZ treatment gives an impression of the effect of this medicine. However, this possibility is remaining because there was no serial scoring data before TCZ treatment. Third, concomitant medicines might effect ROM improvement. Methylprednisolone and bosentan were used as concomitant medicines. Bosentan in

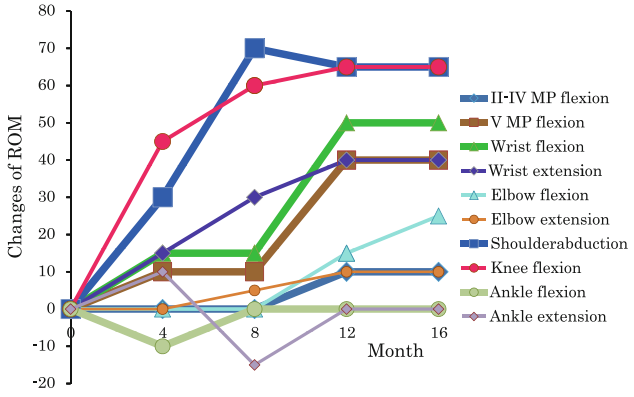

Fig. 1 Impact of tocilizumab (TCZ) on joint mobility in a patient with SSc. Joint range of motion (ROM) was initially set to zero, and data are expressed as the degree of improvement during the 16-month TCZ therapy. The *horizontal axis* indicates months after TCZ initiation. All ROM values, except for those in the ankles, improved considerably after 4 months and continued to improve until the end of study. The *unit* of angle is degrees

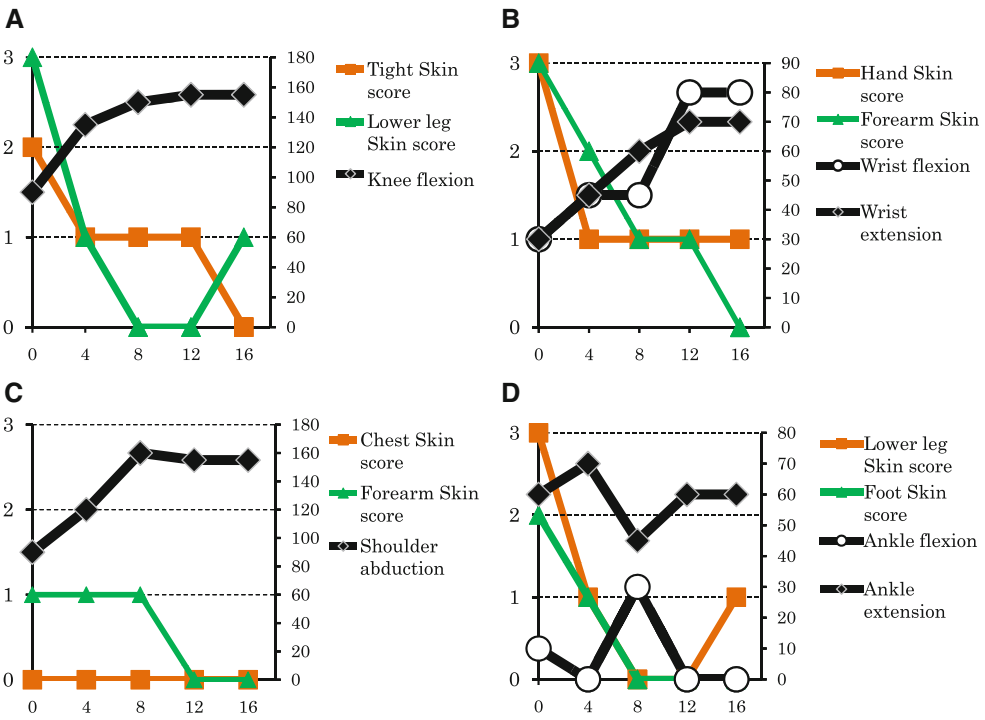

Fig. 2 Relationship between joint mobility and skin sclerosis in a SSc patient during TCZ treatment. The *left vertical axis* indicates the modified Rodnan total skin score, and the *right vertical axis* indicates ROM value. The *horizontal axis* indicates months after TCZ initiation. The skin scores for the knee (**a**), wrist (**b**), and shoulder (**c**) joints decreased as the ROM increased. In contrast, the ROM of the ankle joint did not improve, even though the skin scores of the lower leg and foot decreased to 0 after 8 months (**d**)

particular might contribute to reduction of skin score, because bosentan has protective efficacy for skin ulcer in SSc [8]. The possibility that bosentan acts to improve ROM might remain, but there is no report which presents an effect of bosentan on ROM improvement. The reason why the ROM of the ankle joints remained unchanged is unclear. There may be a relationship with long-term wheelchair use. This patient also had kidney, heart, and bowel involvement, and it is unclear how they were affected by TCZ administration. Although she has remained free from dialysis or home parenteral nutrition to date, she continues to require angiotensin receptor blockers, proton pump inhibitors, diuretics, and antibiotics. There is a possibility that the internal organ symptoms are being affected by these medications. TCZ administration, however, clearly resulted in improvement in the skin score for this case as well as former reported cases [7], and in this case, it was clear that the skin score decrement after TCZ initiation was not because the skin became easy to pinch but because the tissue was becoming soft and easy to move.

There is currently no standard pharmacological guideline for treatment of SSc, despite numerous clinical trials on steroids, antirheumatic drugs, and immunosuppressive agents. While an effective low-dose corticosteroid therapy with prednisolone has been proposed for early-phase diffuse cutaneous SSc [9], patients are at risk of developing sclerodermal renal crisis [10]. The effectiveness of penicillamine in SSc treatment remains controversial [11]. On the other hand, the European League Against Rheumatism recommends methotrexate for treatment of skin sclerosis in patients with early diffuse SSc [12], but an opposing view was also presented [13]. Other immunosuppressive agents such as cyclophosphamide, cyclosporine A, tacrolimus, and mycophenolate mofetil have been evaluated for treatment of SSc. Though the beneficial effects of one-year oral administration of cyclophosphamide on skin thickening have been reported [14], the long-term safety of this medicine has not been verified. There are no data which present late-occurring toxicities of cyclophosphamide in patients with SSc, but there are several reports which present oncogenicity after withdrawal of this medicine in patients with systemic lupus erythematosus and rheumatoid arthritis [15]. The usefulness of cyclosporine is also controversial because of the associated risk of sclerodermal renal crisis [16, 17]. The effectiveness of mycophenolate mofetil as an immunosuppressive agent in SSc treatment also remains inconclusive [18, 19], though a recent study presented beneficial effects in patients with recent-onset SSc [20]. Finally, several biologic agents are currently being evaluated for treatment of skin involvement in SSc, of which only rituximab has shown efficacy [21, 22]. Therefore, effective treatment for this disease is an ongoing challenge.

The effect of TCZ on skin sclerosis, pneumonitis, or the other symptoms in patients with SSc remains unclear, and further studies are required to verify this. The efficacy of TCZ for patients with SSc is currently being evaluated in an open-label trial in Japan (UMIN0000055550) and a double-blind trial in Europe and North America (NCT01532869); the results of these trials should provide further information on unresolved issues.

In this report, we described time-course changes of ROM observed in a patient with SSc during treatment with TCZ. The relation between TCZ treatment and ROM changes observed in the patient is currently unclear.

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Conflict of interest T. Kishimoto holds a patent for TCZ, and receives royalties for ACTEMRA®. A. Ogata received a consulting fee from Chugai Pharmaceutical Co. Ltd. for providing medical advice. Other authors have no conflict of interest to declare.

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